Electron-deficient Alkyne Lipids Enable Efficient Synthesis of Comparable Polymer Lipids via Copper-free Azide-Alkyne Cycloaddition

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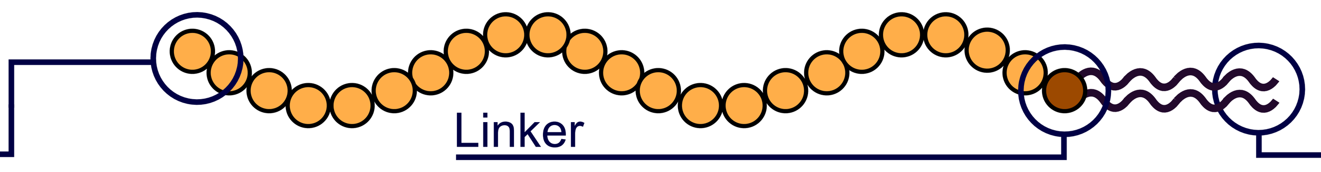
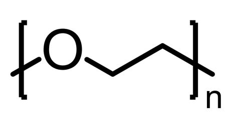
Hot Paper in Angewandte Chemie!

Motivation

Polymer lipids are essential components of liposomes and lipid nanoparticles for drug and gene delivery, providing colloidal stabilization and defining the biological interface.[1]

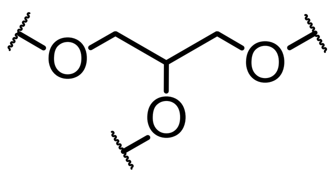


Hydrophilic Polymer

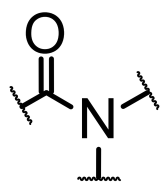


PEG is the current gold standard and alternatives are difficult to access.

Linker

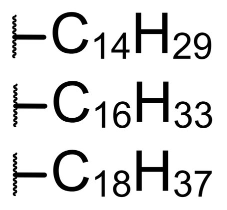


The large structural variety potentially reduces the comparability.



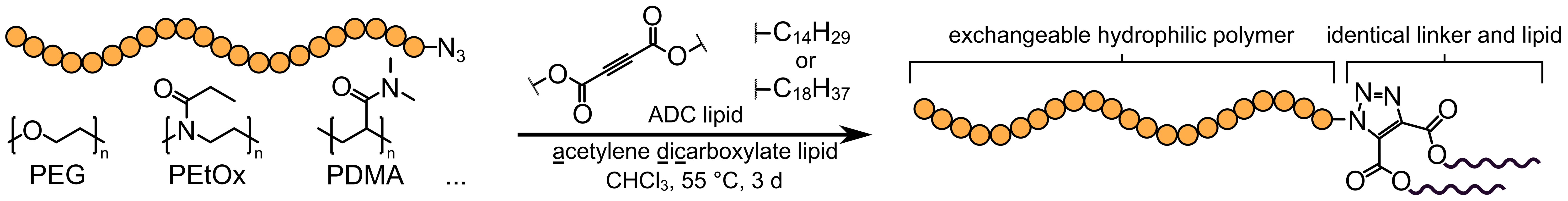
Lipid Moiety

The most commonly used two linear, saturated alkyl chains require a more complex linker structure and synthesis.



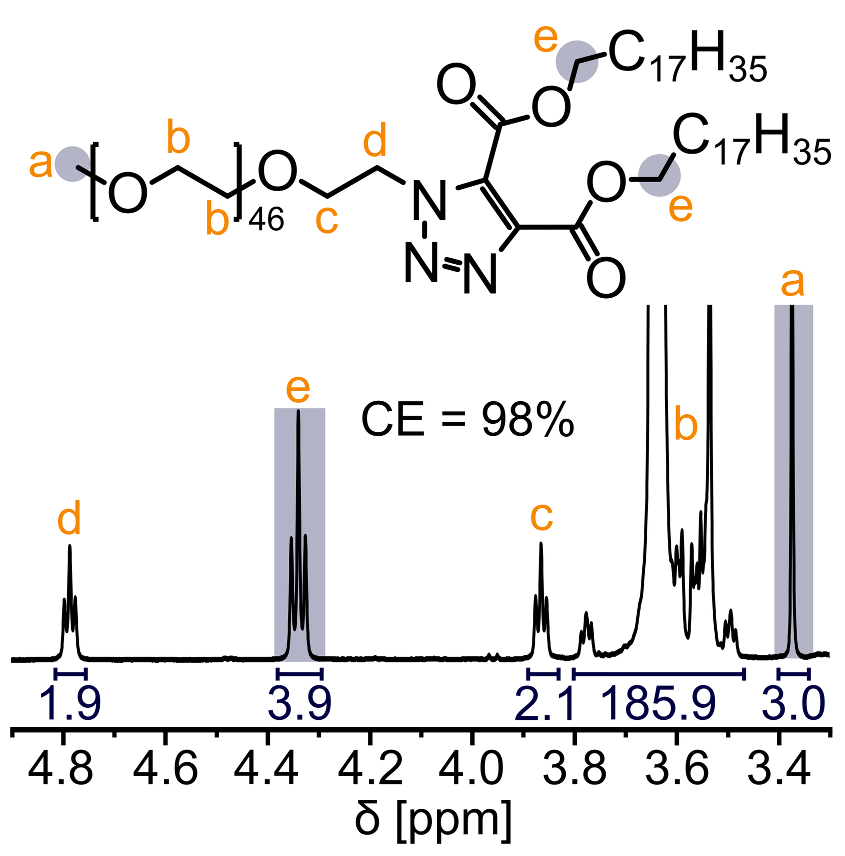
To understand the influence of the polymer lipid structure on the behaviour of lipid-based carrier systems *in vivo*, we need access to comparable polymer lipids.

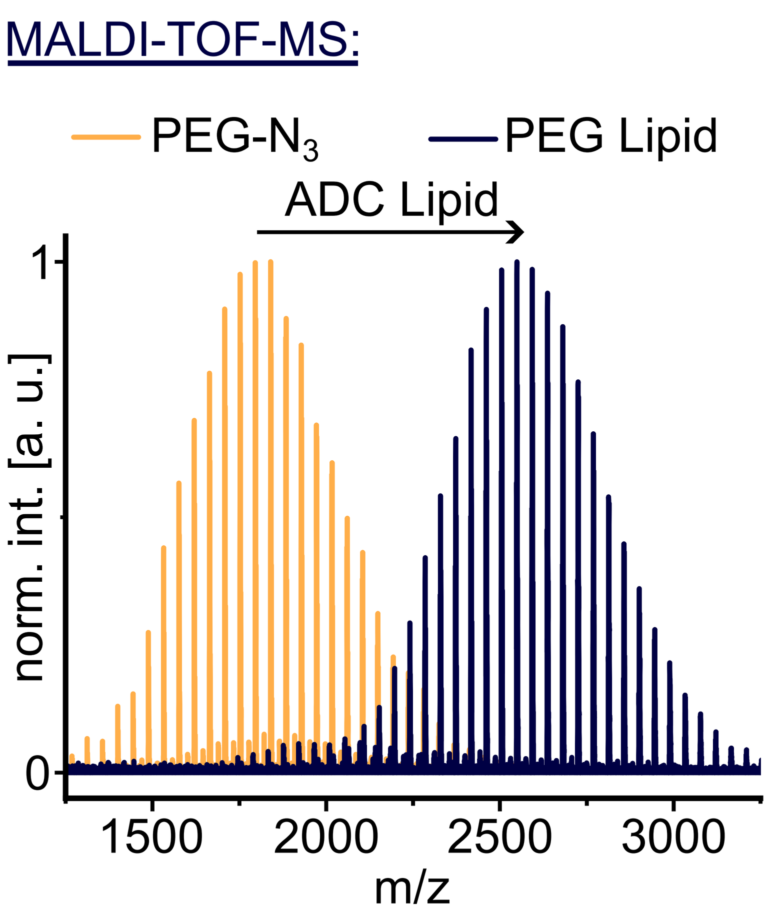
Synthesis Approach



Our catalyst-free approach with 100% atom-efficiency yields highly comparable polymer lipids. It is compatible with a wide range of hydrophilic polymers and allows tuning the lipid chain length.

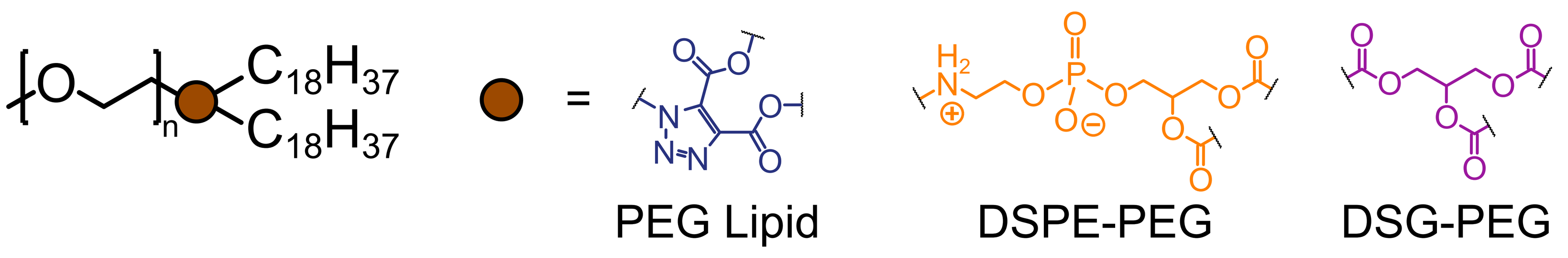
Characterization

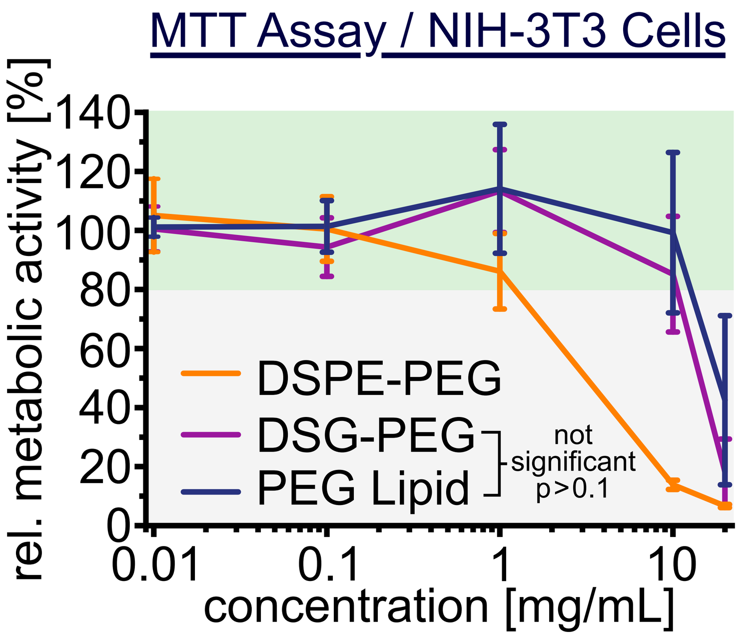


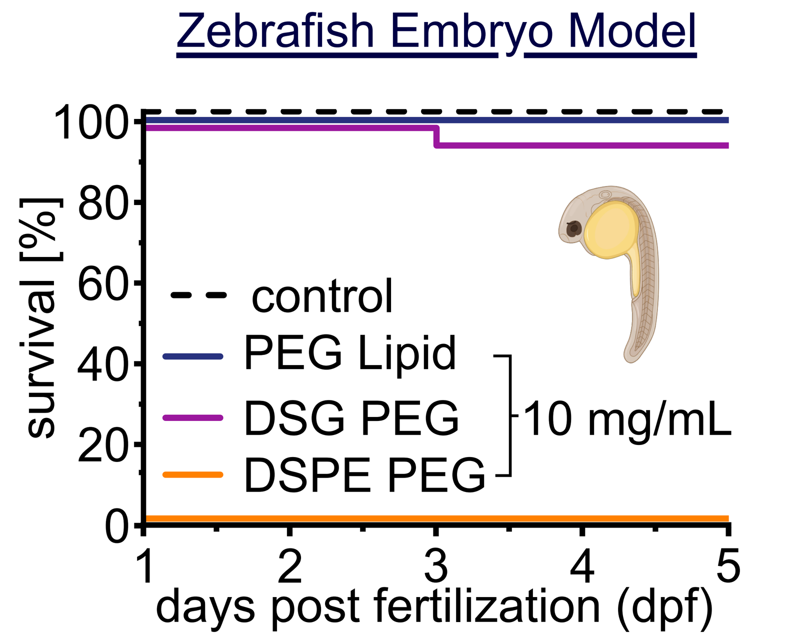


We achieve quantitative coupling efficiencies (CE) with high yields ≥ 70% for all polymers.

Toxicity Studies

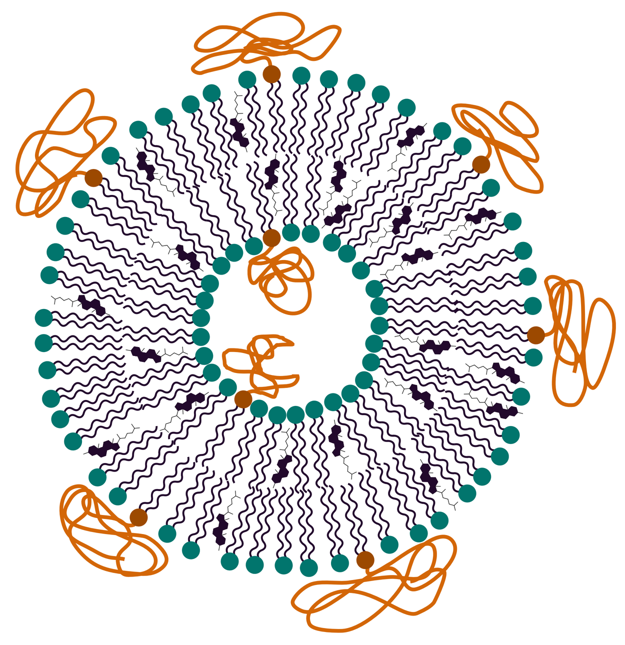


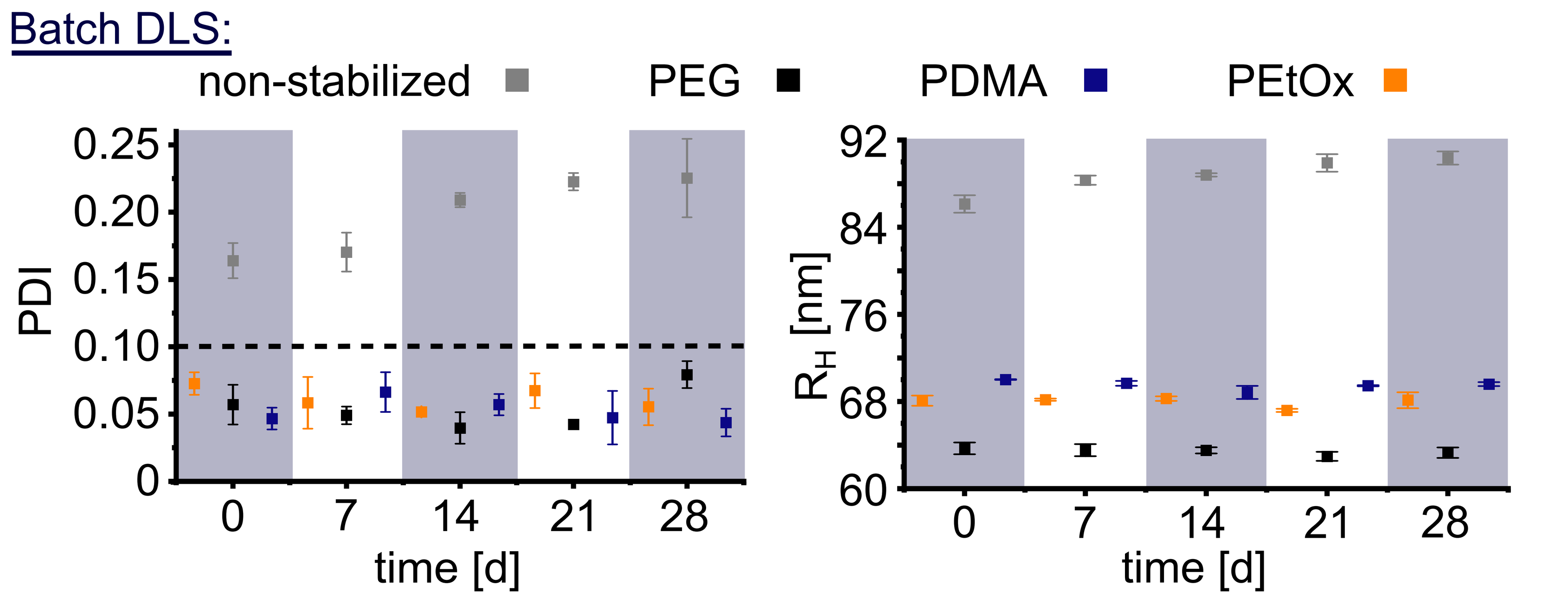


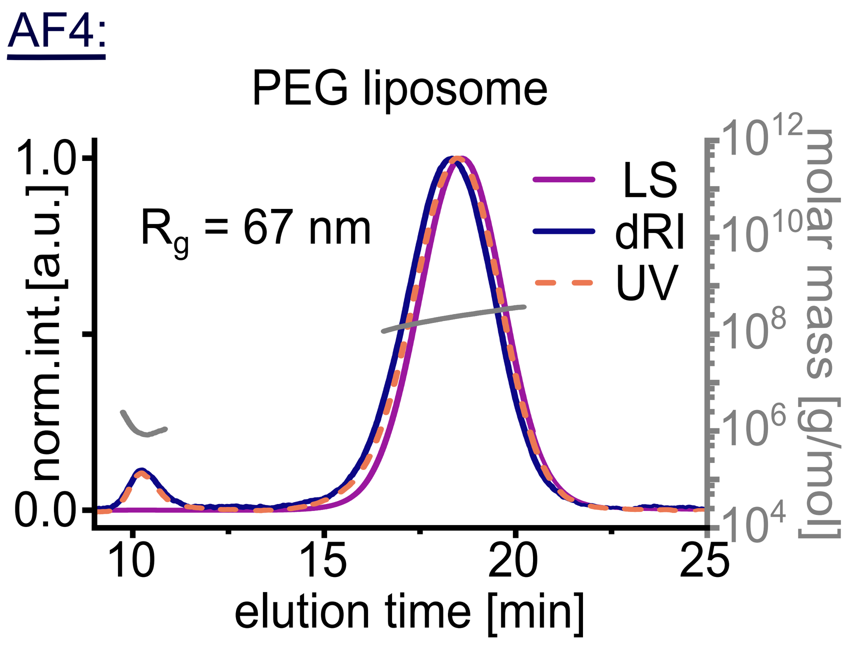


The toxicity profile of our linker is similar to industry standard linkers in *in vitro* and *in vivo* experiments.

Liposome Preparation





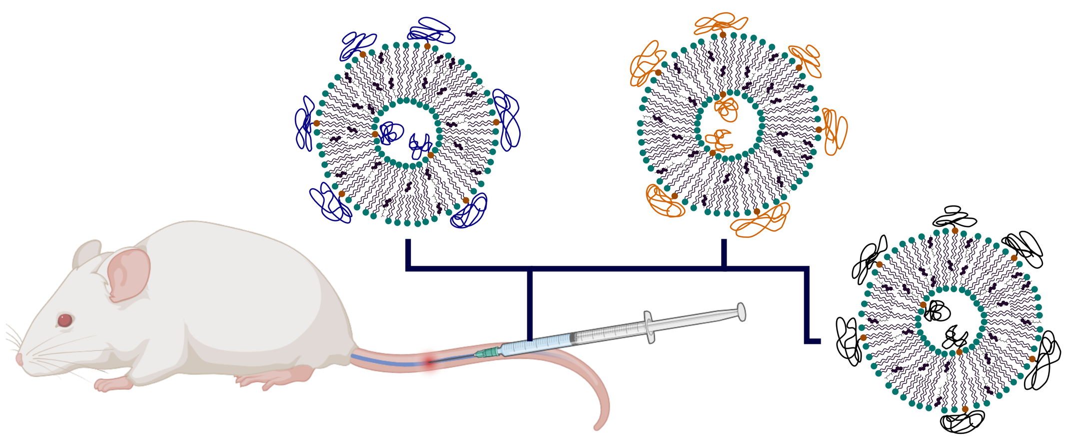


All obtained polymer lipids enable the preparation of well-defined and stabilized liposomes.

Conclusion and Outlook

Here we present an efficient and versatile synthesis approach, yielding highly comparable polymer lipids with identical linker and lipid structure.

We are looking to build on the promising initial results with detailed comparison studies on the behaviour of lipid-based carrier systems *in vivo*.



- circulation time
- immunogenicity
- biodistribution

References

[1] J. S. Suk et al. Adv. *Drug Deliv. Rev.* **2016**, *99*, 28-51.

[2] F. T. Kaps et al. *Angew. Chem. Int. Ed.* **2025**, e202501262.

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